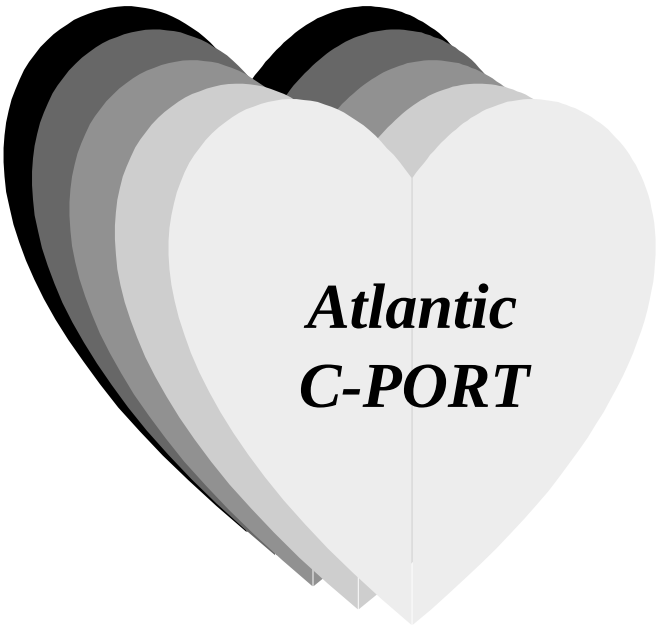
The

Atlantic C-PORT Trial



Elective Angioplasty Study

Manual of Operations

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1 - Background

Background

Percutaneous coronary intervention (PCI) developed at tertiary institutions which had both active cardiac catheterization laboratories and active cardiac surgery programs. Initially, a significant number of PCI patients (14% in Gruentzig first 50 cases) required emergency cardiac surgery because of unanticipated, procedure-related complications which included abrupt closure, coronary dissection and coronary perforation. Over time, with increasing levels of operator experience, better patient selection and improved catheter and wire design, the rate of complications requiring emergency surgery declined, reaching levels of 3 to 4 % by the late 1980's and the beginning of the 1990's. With the further improvements in catheter and wire design, the advent of coronary stents and increasing knowledge regarding safe and effective antiplatelet and anticoagulation regimens and their appropriate monitoring, PCI became an increasingly safe and effective procedure. Currently, emergency CABG rates of less than 0.2% are commonly reported (1)

Arguably, today coronary perforation is the most important, life-threatening complication requiring emergency surgery. For patients treated with balloons and stents alone, current emergency surgical rates for perforation are in the range of 0.1 % (2). For patients treated with niche devices (eg. laser or rotational atherectomy, directional atherectomy, etc) and patients with high risk lesions emergency surgical rates, and complications in general, are higher (2).

The marked decline in the use of emergency cardiac surgery following failed PCI has led to performance of elective PCI without formal cardiac surgical backup in nearly all institutions (i.e. there is no cardiac operating room open, available and staffed for treating PCI-related complications). Indeed, elective PCI is frequently performed well into evening, nighttime and weekend hours, when cardiac surgical personnel are not in hospital.

The marked decline in the need for emergency cardiac surgical services and the fact that formal surgical standby is no longer practiced, have led to the idea that on-site cardiac surgery is no longer required for most patients undergoing PCI. The apparent benefits of primary PCI over thrombolytic therapy (3) motivated the extension of primary PCI capability to hospitals without on-site cardiac surgery. Based on the C-PORT Primary PCI trial (4) and other studies, several states (eg. Massachusetts, New Jersey, Michigan and Maryland) allow primary PCI at hospitals without SOS.

Because adverse event rates are so low, and due to the success and acceptance of primary PCI at hospitals without SOS, performance of PCI in other patient groups at hospitals without SOS is gaining wider acceptance. Most registry reports (5-8) suggest that elective PCI can be performed safely and effectively at such hospitals, while others suggest low volume hospitals (less than between 50 and 100 cases per year) should not perform non-primary PCI without SOS (9). In some studies, the time to get to an operating room from the catheterization laboratory in a hospital without SOS is no longer than that required in a hospital with SOS (10). Other studies demonstrate a longer time to the operating room from hospitals without SOS, but no difference in CABG outcome (7). Yet, despite these encouraging early results, the ACC/AHA Guidelines for performance of PCI suggest more data are needed to decide whether elective PCI can be safely and effectively performed without on-site cardiac surgery (11).

There are many motivations for performing elective PCI at hospitals without SOS. One most often heard and used in a pejorative way is the financial motivation: that is, hospitals currently without elective PCI capability want to have that capability in order to improve or maintain the hospital's 'bottom line'. But this argument, which is meant to be disparaging, is trite, myopic and can be applied to hospitals with and without SOS. For these reasons, it should be ignored as an argument for or against extension of elective PCI to hospitals with SOS. A hospital not concerned about

its finances, not acting in a way to improve or maintain its fiscal well-being, is not likely to survive. Again, this is true for hospitals with and without SOS.

Other commonly-mentioned motivations for performing elective PCI at hospitals without on-site cardiac surgery include reduced bleeding (avoiding transfer of patients with intravascular sheaths in place), patient and family preference and satisfaction, physician convenience, and reduced cost (by avoiding transfer to other facilities and, potentially, additional hospital days if PCI is delayed) (6).

There are in addition to these rather superficial, though not inconsequential, reasons, deeper and more complex motivations for considering elective PCI at hospitals without SOS; motivations related to patients outcomes, access and safety.

One important motivation is to sustain primary PCI programs at hospitals without SOS. Primary PCI improves patient outcomes and reduces adverse events in patients with ST-segment elevation myocardial infarction (STEMI). Because most patients with STEMI present to hospitals without SOS, timely access to primary PCI and patient outcomes are improved by extension of primary PCI capability to hospitals without SOS. Sustaining stand-alone primary PCI programs can be difficult both financially and in terms of required human resources. The ability to perform elective PCI can help assure maintenance of these important programs and may refine expertise by increasing volume.

Although there is a general consensus that most patients have adequate access to interventional services, studies which actually measure utilization of these services often find significant underutilization for patients with acute and chronic coronary syndromes who present to hospitals without PCI capability (12-15). Patient who come to so-called spoke hospitals and who would benefit from transfer to a hub hospital for invasive and interventional services, are frequently not transferred. This failure to utilize interventional services translates into worse patient outcomes including increased mortality and morbidity. Thus, while regionalization and centralization of services may seem like a good idea, it, in fact, does not work. It, in reality, restrict rather than expands access to appropriate interventional care. The reasons why physicians fail to transfer patients who may benefit is unclear and is likely to be complex and multifaceted, but could include a desire to maintain care of the patient, a reluctance of the patient to be sent to an unfamiliar facility for care by unknown providers, a reluctance of the family to allow transfer to a more distant, larger and unfamiliar hospital, and certainly many other possible reasons. The fact that this identical issue is seen within the regionalized Veterans Administration Hospital system (14) suggest financial considerations do not account for failure to transfer and underutilization. Extension of elective PCI capability to hospitals without SOS may increase access to appropriate care and reduce morbidity and mortality among patients with a variety of acute and chronic coronary syndromes.

Because PCI has become an increasingly important part of acute and chronic coronary artery disease treatment, it is increasingly difficult to recruit and retain excellent cardiologists, both interventional and non-invasive, at hospitals not capable of providing interventional services. Lack of PCI and the creation of regional centers-of-excellence create, *de facto*, second and third tier facilities or centers-of-less-than-excellence. Some cardiologists do not want to practice in such a setting. Because cardiology services are required ubiquitously in a hospital, failure to have excellent cardiologists can reduce the standard of care for patients on non-cardiology services. Extension of elective PCI capability to hospitals without SOS will help maintain and may improve cardiology care throughout an institution, including on non-cardiology services.

From a healthcare policy standpoint, pressure to create more cardiac surgery program just to “back up” elective PCI programs is problematic, particularly since the volume of cardiac bypass procedures is flat or decreasing, even as the population at risk increases.

Finally, from a health policy point-of-view, it may be helpful to be able to dissociate cardiac surgical and coronary interventional services so that the pressure to create more surgical programs just to back-up interventional program is reduced. At a time when the number of coronary bypass surgeries is declining, it seems appropriate to

expand the number of bypass programs for only the most compelling of reasons. Support of elective PCI is probably not one of them.

Irrespective of motivation, the fact is that more and more institutions are performing elective PCI without SOS in states where co-location of cardiac surgery and PCI is not required (6), and pressure to allow elective PCI without SOS continues to grow in states where co-location is required by regulation. National guidelines (11) continue to state that elective PCI without SOS should not be routinely performed until research clearly demonstrates equivalent safety and efficacy compared with outcomes in centers with SOS. What is required now is good scientific evidence. The universally agreed upon need for additional research in this area is, itself, among the strongest motivations for pursuing this clinical trial.

The proposed study addresses two critical and interrelated issues related to performance of PCI without SOS: 1. Can PCI be performed safely and effectively at hospitals without SOS? 2. Under what conditions is this possible? Both *what* is done and *how* it is done are of equal importance.

2 - *Study Objectives and Protocol Outline*

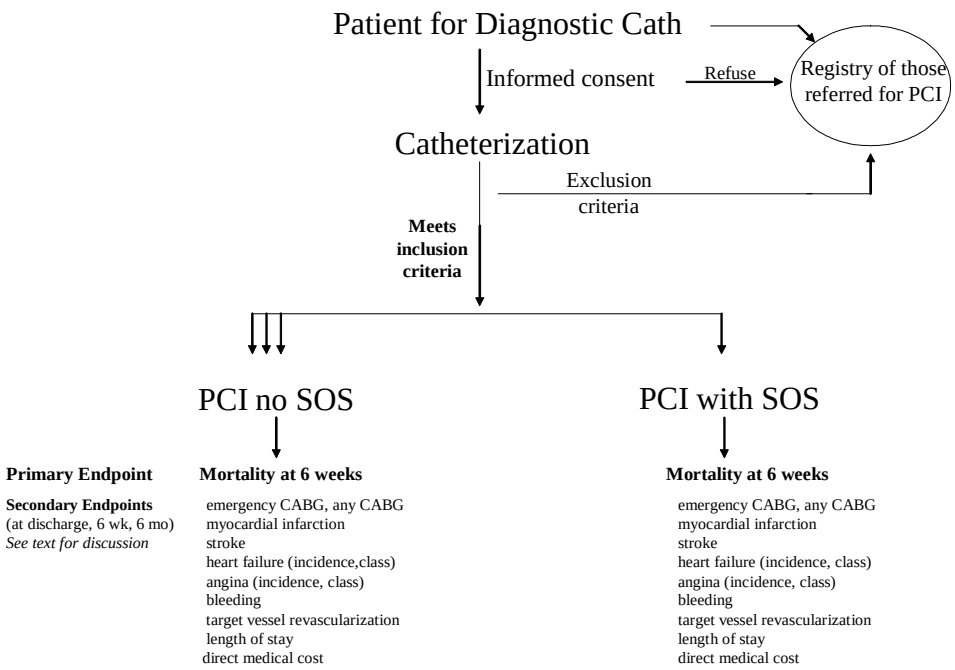
I. Study Objectives

This study tests the hypothesis that outcomes of elective PCI performed at hospitals without SOS are not inferior to outcomes of PCI performed at hospitals with SOS.

The **specific aims** of this project are demonstration that in patients randomly assigned to have elective PCI at a hospital without SOS

a. the incidence of death is not greater
b. the incidence of myocardial infarction, stroke, bleeding, heart failure, target vessel revascularization (TVR) is not greater
c. the incidence and classification of heart failure and angina are not greater
d. angiographic and clinical success rates are not lower in a subset of patients
e. the direct cost of care for the PCI is not greater

than in patients undergoing elective PCI at hospitals with SOS. The primary endpoint is mortality 6 weeks after index PCI.



II. Protocol A schematic of the study protocol is shown in the figure to the left. The study population is patients undergoing diagnostic cardiac catheterization for suspected coronary artery disease (CAD) at hospitals without SOS. Prior to catheterization potential study subjects are approached for participation in the trial and informed consent is obtained. Subsequently, patients undergo routine diagnostic catheterization, as clinically indicated. After diagnostic catheterization and prior to randomization, post-catheterization inclusion and exclusion criteria (see below) are used to determine whether the patient can undergo PCI at the hospital without SOS. If the patient subject has no post-catheterization exclusions, then he is randomized to either remain at that hospital for PCI or be transferred to a hospital with SOS (the "usual care" group). Randomization is not symmetric but is instead 3:1, so that for every four eligible study subjects, three undergo PCI at the hospital without SOS and one has PCI at the hospital with SOS.

Patients refusing to participate in the randomized trial are asked to participate in an outcomes registry of individuals who have diagnostic catheterization at the hospital without SOS and, if indicated, have subsequent PCI at

hospitals with SOS. This registry will help determine whether and to what extent selection bias occurs in the trial. Similarly, study subjects who sign informed consent but who after catheterization do not meet inclusion criteria or have exclusion criteria are followed in a PCI registry of non-randomized patients. Whether it is possible to capture outcomes of patients never approached for inclusion in the project is not clear, but is desirable. Efforts will be made identify and follow these individuals for simple outcomes.

Details of primary and secondary endpoint selection, data definitions and collection and analysis are below. The primary clinical endpoint is the incidence of death 6 weeks after index PCI. The primay economic endpoint will be total medical costs at 6 weeks. Secondary endpoints include incidence of emergency coronary artery bypass surgery (CABG), myocardial infarction, stroke, target vessel revascularization, bleeding, and incidence and class of heart failure and angina, total medical costs at discharge and 6 months, and major resource consumption patterns. All endpoints are measured at hospital discharge, 6 weeks and 6 months after index PCI. In a subset of patients at all sites (with and without SOS) angiographic success and angiographic complications are measured.

3 - Patient Eligibility and Identification

I. Patient Eligibility

Study Population The patient population includes inpatients and outpatients undergoing diagnostic cardiac catheterization for suspected coronary artery disease (CAD) at hospitals without SOS.

Patient *inclusion* criteria are

Pre-catheterization

1. must be undergoing diagnostic cardiac catheterization for suspected CAD
2. be at least 18 years of age
3. must not be pregnant or must not be of childbearing potential
4. must be able to give informed consent.

Post-catheterization

5. coronary artery disease judged to be clinically and angiographically significant
6. ability to perform PCI with equipment available at the local site
7. procedure risk judged to be not high

Patient *exclusion* criteria are

Pre-catheterization

1. inability to give informed consent
2. ST-segment elevation myocardial infarction
3. pregnancy

Post-catheterization

4. high likelihood of requiring a device not available at the hospitals without SOS
5. no need for PCI
6. need for coronary artery bypass surgery
7. high procedural risk (see below)

High procedural risk criteria are

1. PCI of unprotected left main coronary artery
2. PCI of left circulation lesion in the presence of critical (>70%) unprotected left main coronary artery lesion
3. poor left ventricular function (EF≤ 20%) *and* need to perform PCI in a vessel supplying significant myocardium

II. Patient Identification

The intent of the project is to identify and approach for study participation all consecutive patients presenting to participating hospitals for diagnostic catheterization for suspected or known coronary artery disease.

Responsibility for identification of patients that may be candidates for the trial rests primarily with catheterization laboratory staff, although this may vary from institution to institution. All patients undergoing diagnostic catheterization refusing to participate in the study will be asked to participate in a registry. The purpose of the registry is to define characteristics of patients who did *not* participate in the study so that selection bias can be defined.

Once a patient is identified (meets all inclusion criteria and has no exclusion criteria), the patient undergoes diagnostic cardiac catheterization. If the patient does not require revascularization, requires revascularization not available at the no-SOS hospital (either PCI with a device not available or CABG), or is judged high risk (see above), then the patient is not randomized. Un-randomized patients excluded post-catheterization will be followed and outcomes recorded in a registry.

4 – Institution, Physician and Device Criteria

In addition to patient inclusion and exclusion criteria, there are institutional, physician and device criteria for participation.

Participating Site Inclusion Criteria: Participating sites are required to enter into a formal contractual arrangement with the Clinical Coordinating Center. This agreement includes financial arrangements between the participating site and the Clinical Coordinating Center related to program development and data collection, and details work the Clinical Coordinating Center performs for the participating site.

Participating sites must meet the following inclusion criteria:

1. capability of performing a minimum of 200 PCI's (elective + primary) per year in an existing laboratory (this may be modified by specific State requirements)
2. agree to complete an elective PCI development program (and a primary PCI development program if not already completed)
3. agree to abide by the study protocol and to physician, patient and device selection criteria defined in the Manual of Operations
4. agree to collect and transmit study data in a timely fashion
5. agree to develop and maintain a quality and error management program, including a weekly interventional conference and monthly QE review
6. perform primary PCI 24/7 with reporting of outcomes in a parallel registry
7. develop and maintain necessary agreements with a tertiary facility (which must agree to accept emergent and non-emergent transfers of enrolled patients for additional medical care, cardiac surgery or intervention)
8. develop and maintain agreements with an ambulance service capable of advanced life support and IABP transfer that guarantees a 30-minute-or-less response time
9. except as provided by alternative State regulation, there must be a proven, practiced plan for removal of a patient from the hospital without SOS to a hospital with cardiac surgery within 60 minutes of initiating the call for emergency transfer (exceptions may be made for certain, particularly rural, settings)

Participating Physician Inclusion Criteria:

Interventionalists who wish to participate in this project must meet the following criteria:

1. meets the ACC/AHA standards for competency (minimum of 75 cases per year)
2. agrees to practice in accordance with the study-defined device and patient selection criteria
3. agrees to obtain necessary informed consent for patient participation in this project
4. agrees to necessary data form completion
5. agrees to participate in the elective (and primary, if necessary) development program
6. agrees to abide by the study protocol defined in the Manual of Operations
7. agrees to participation in the QE management program
8. agrees to participate in the weekly interventional conference

Device Selection Criteria:

The following devices will be excluded from use:

1. any atherectomy device
    a. rotational atherectomy
    b. directional atherectomy
    c. laser atherectomy
    d. excisional atherectomy
    e. use of cutting balloons except within stents for in-stent restenosis

5 – Study Design and Study Endpoints

I. Study Design

The study is designed as a patient-outcomes oriented, un-blinded, active-control, non-inferiority trial with asymmetric randomization. Angioplasty program development (both elective and primary) is necessary at all hospitals without SOS.

Choice of Study Design:

Several principles guided the choice of design for this trial. First, because results of this study may influence health care policy affecting care of hundreds of thousands patients, it should furnish results of the highest quality. Second, and for similar reasons, the primary outcome measure should be both clinically meaningful and unambiguous. Third, secondary outcomes are not secondary in importance but importantly determine interpretation of study results. Fourth, the study should be as 'real world' as possible, with minimal or no protocol-driven care so that its application to clinical practice is as general as possible. Finally, the study must clearly define the circumstances under which PCI without SOS is safe and effective. This is done not only by clearly specifying patient, practitioner, institutional and device inclusion and exclusion criteria, but also by defining the formal PCI development program each institution without SOS completes prior to project implementation.

A randomized trial design was chosen over a registry because it furnishes the highest quality data in the most meaningful and unambiguous way. A registry offers inferior quality data because of problems common to all registry data: selection bias compounded, in this particular instance, by marked heterogeneity of the population under study. Randomization allows comparison between two groups (those undergoing PCI at hospitals with and without SOS) whose patient populations are less affected by selection bias or heterogeneity that importantly affect clinical outcomes.

Hospitals without SOS may have relatively low yearly PCI case volumes; compared with a registry, a 1:1 randomization scheme reduces that yearly volume by half. The asymmetric, 3:1 randomization scheme is chosen to minimize the effect of randomization on PCI volume at hospitals without SOS.

The desire to design a "real-world" study is balanced by the goal of minimizing the potential for harm. Protocol-driven care is eliminated or minimized, while patients considered at 'high risk' are not enrolled and devices associated with high complication rates are eschewed. Other study features that may minimize the potential for harm include interventional practitioner and institutional volume requirements which match the minimums set forth by the ACC/AHA guidelines.

II. Study Endpoints

Primary Outcome:

The choice of study endpoints is crucial in any trial, and is particularly so in this non-inferiority study whose outcomes may help define health care policy that can affect care of a large number of patients. Recognition of this leads to setting "standards" the chosen primary endpoint must meet that reflect the potential importance and influence study results may have. These characteristics or standards are:

1. the occurrence of the primary outcome cannot be obscured
2. the definition of the primary outcome must be unambiguous and clinically meaningful

3. the primary outcome must be the *sine qua non* of non-inferiority. That is, if the primary outcome fails to demonstrate non-inferiority (or superiority) of elective PCI in hospitals without SOS, then the entire study fails to support elective PCI in hospitals without SOS no matter what ***any*** other outcomes demonstrate.

Note that standard three does not mean that secondary outcomes are unimportant. Nor does it mean if the primary outcome demonstrates non-inferiority of elective PCI in hospitals without SOS, then that should become health care policy regardless of other outcomes.

The outcome which meets these standards best is death. It is a 'difficult' endpoint to choose because its incidence is relatively low, making the estimated sample size for this project relatively large (see below). But its advantages outweigh its disadvantages when viewed from the perspective outlined above.

The conventional primary outcome for studies like this one is a "composite" endpoint whose main virtue is that it increases the 'event' rate and can therefore reduce sample size. In certain circumstances, particularly when the elements of the composite endpoint have identical importance, a composite endpoint may more accurately reflect a clinically important outcome than separate endpoints alone. In this particular non-inferiority trial, all potential elements of any potential composite do not have equal importance and it matters quite a bit which endpoint "drives" or determines the composite.

If mortality is higher in hospitals without SOS but the weight of the other composite endpoints leads to the conclusion that outcomes are not inferior in those hospitals, one would not conclude that healthcare policy should change to allow elective PCI in hospitals without SOS.

A typical composite endpoint in a study like is a so-called "major adverse cardiac event" or MACE rate. A common MACE is the composite incidence of death, emergency coronary artery bypass surgery (CABG) and post-procedure myocardial infarction (MI). These outcomes are not of equal importance. Only in unusual circumstances would emergency CABG and post-procedure MI be given a clinical importance or weight equal to death. In addition to the problem of clinical inequality among composite MACE elements, the definition of elements other than death is often arbitrary and ambiguous. For example, measurement of post-procedure MI is meant to detect myonecrosis caused by the procedure itself or by failure to complete the procedure successfully. As many as 70% of study patients will have some form of acute coronary syndrome (ACS) and will be sent to 'early invasive' diagnostic catheterization. Such patients may enter the study with a first set of cardiac biomarkers that are normal and a second set, post-procedure, that indicates myonecrosis. Is this a result of the procedure or the ACS? Furthermore, definitions of a significant MI based on ECG changes or percent elevations of a biomarker above normal are necessarily arbitrary.

In addition to ambiguity in the definition of MACE elements other than death, the very event rate observed may be modified by the location of the PCI. For example, emergency CABG rates are lower at hospitals without on-site surgery (8). Is this because surgery tends not to be used when not immediately available? Is this better medical care of inappropriate underutilization? Does it lead to better or less favorable outcomes other than death (eg. heart failure)? How well can we actually distinguish emergency CABG undertaken for non-procedure-related reasons from those undertaken because of a PCI complication; or surgery simply performed quickly because it is clinically appropriate and available within 24 hours of study entry? There is both ambiguity in the definition of "emergency CABG" as an endpoint and a potential effect of procedure location on its observed occurrence.

Other potential composite MACE elements suffer from either or both of these flaws: their occurrence is not clinically equivalent to death, their definition is ambiguous, their occurrence may be unintentionally obscured.

Secondary Outcomes:

Secondary outcomes are only 'secondary' because they fail to fulfill all the criteria for the primary endpoint. They are *not* of secondary importance. Indeed, secondary outcomes importantly influence interpretation the primary outcome, assist application of study results to clinical practice and healthcare policy making, and may help generate additional hypothesis.

Secondary outcomes that will be measured at discharge, 6 weeks and 6 months include but are not limited to

a. emergency CABG
b. myocardial infarction
c. target vessel revascularization (TVR)
d. heart failure and class
e. angina and class
f. stroke
g. composite adverse endpoint (MACE)
   MACE = death + emergency CABG + MI + stroke
h. angiographic (procedural) complications
i. angiographic (procedural) success (<20% residual stenosis and TIMI 3 flow)
j. Clinical success
   clinical success 1 = angiographic success AND no MACE AND no TVR
   clinical success 2 = no/improved angina AND no/improved heart failure AND clinical success 1
k. bleeding (non-CABG transfusion, vascular repair)
l. vascular repair procedures (surgery, pseudoaneurysm compression)
m. length of stay
n. total direct medical cost
o. major resource consumption patterns (hospital and ICU days, surgeries, hospitalizations)

6 – Sample Size and Feasibility

I. Sample Size

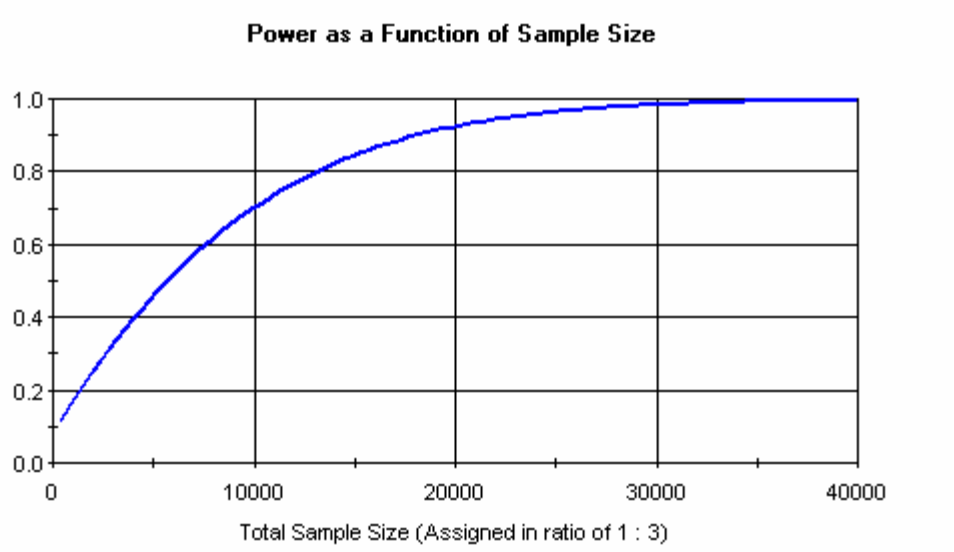
This is a non-inferiority trial. In a non-inferiority trial the expected event rate for the primary outcome is estimated, and a margin selected which defines non-inferiority. Actual data from the New York State (16) and the NHLBI DYNAMIC (17) angioplasty registries are used to estimate expected event rates. The actual observed variation in the event rate among hospitals in these registries is used to define the margin. The standard deviation gives an estimate of "acceptable" variation in observed mortality among institutions.

Event rates vary depending on the types of patients undergoing PCI. In this study, only patients with ST-segment elevation MI (STEMI) are excluded from randomization (they are followed in a separate registry); non-ST-elevation MI (NSTEMI) patients are included in the randomized trial. Based on NYS registry data, about 29% of patients have stable angina, 63% unstable angina and 9% acute MI. Patient distribution is similar in the DYNAMIC registry.

Registry	Mortality	Standard Deviation
New York State	0.0086	0.0083
DYNAMIC	0.0140	0.0092
Average	**0.0113**	**0.0088**

To estimate sample size for this trial, conservative assumptions are made. The chosen point estimate for mortality is 1.0 %, somewhat lower than the average of the observed mortality rates in the two registries. Note that this number represents mortality at hospital discharge and is probably still lower than mortality at 6 weeks, when the primary outcome is actually measured. In addition, the margin selected is 0.005, which is less than one standard deviation of the observed mortality rates among institutions participating in either the NYS or DYNAMIC registries. Sixty-seven percent of sites in the registries above reported an observed mortality within one standard deviation of the mean mortality. Using this as a margin seems reasonable since this is the variation about the mean mortality considered acceptable. Indeed, some might argue use of more liberal figures may be justified, such as 1.5 or 2 times the standard deviation. The more conservative number was chosen.

Using a one-sided test of significance, and using a 3:1 randomization scheme, approximately 13200 patients are needed in the study (with alpha 0.05 and power of 0.8). Power and sample size is calculated using Power and Precision software version 2.0 (Biostat Inc, Englewood NJ).



This 13200 patient study will have power of 80% to show that the event rate for hospitals without SOS is at least as low as the event rate for those with SOS. The null hypothesis is that the event rate for hospitals without SOS is 0.005 higher than the event rate for hospitals with SOS, and the study has power of 80.4% to reject this null. Equivalently, the likelihood is 80.4% that the 95.0% confidence interval for the difference in event rates will exclude a 0.005 difference in favor of hospitals with SOS.

II. Data Analysis:

The main objective is to assess the non-inferiority of PCI at hospitals without SOS versus PCI at hospitals with SOS. Calculation of sample size is based on the primary end point, mortality. Univariate Poisson regression analysis will be performed to estimate crude relative risks and corresponding 95% confidence intervals. Multivariate Poisson regression model will be used to adjust for potential confounding factors.

Relative risks are considered to be statistically significantly different if 95% confidence interval on the ratio does not include 1. All analyses will be performed on an intention-to-treat basis.

For the economic analysis, for testing of discrete variables, chi square tests or Fisher's exact tests will be used. For testing of continuous variables, nonparametric statistical tests will be used, such as the Wilxcoxon rank-sum test.

The mean between-treatment-group differences in medical costs based on 1000 bootstrap datasets will be estimated, and estimate a 95% confidence interval (CI), and calculate the percentage of samples in which PCI in a non-SOS facility is cost-saving versus PCI in a SOS facility. The primary analysis will use a societal perspective, although all costs are not included.

III. Feasibility

Assuming 40 institutions are involved and that each performs at least 150 elective PCIs per year (the other 50 are primary PCI's), then 12000 patients can be recruited in two years. Since many centers will perform more than the minimum number, a shorter recruitment time is expected. The C-PORT study has developed primary PCI at more than 40 hospitals. It is anticipated that some of these hospitals, and other hospitals not currently in C-PORT, will participate in this trial.

7 - Consent Procedures

I. Informed Consent

Informed consent must be obtained prior to diagnostic catheterization on all study patients. Verbal consent or consent obtained during a cardiac catheterization is not allowed. Informed consent must be obtained at the hospital where catheterization takes place and requires IRB approval of that institution. Obtaining informed consent at a non-participating hospital where diagnostic catheterization is performed in anticipation of possible transfer to a participating hospital without SOS for PCI as part of the randomized trial is not encouraged. It is necessary to obtain IRB approval at both institutions if this is considered. Obtaining informed consent for participation in the randomized trial prior to a diagnostic catheterization at a hospital with SOS is not allowed.

The individual obtaining informed consent must be approved and listed with the local IRB. Generally, this will be the invasive cardiologist performing the diagnostic catheterization. The entire consent must be explained to each patient in detail and the patient must have sufficient time to review the consent, ask questions about the study and have those questions answered by individuals authorized by the local IRB to do so, and to consult with any other individuals they may require in order to make an informed decision regarding participation. In the case of potential study-subjects who may not fully understand English, a translator must be provided to review the consent in detail, be available to allow discussion between the investigator-physician and the potential study-subject, and be available for any individuals the potential study-subject may wish to consult during the consent process. In the case of individuals considered not mentally competent or for reasons other than language are unable to give informed consent, surrogate consent may be obtained if and only if specifically allowed by the local IRB for this study from individuals (e.g. next of kin, power of attorney) authorized by the local IRB.

The consent may be translated into other languages if approved by the IRB.

There may be separate consents for the research study and for the procedure (standard procedure consent currently in use at the participating institution). Alternatively, a single consent may be used if approved by the local IRB. All required elements of the standard procedure consent must be incorporated into the research consent if a single consent is used. This includes but may not be limited to information regarding conscious sedation, potential for blood product transfusion and exceptions to anesthesia.

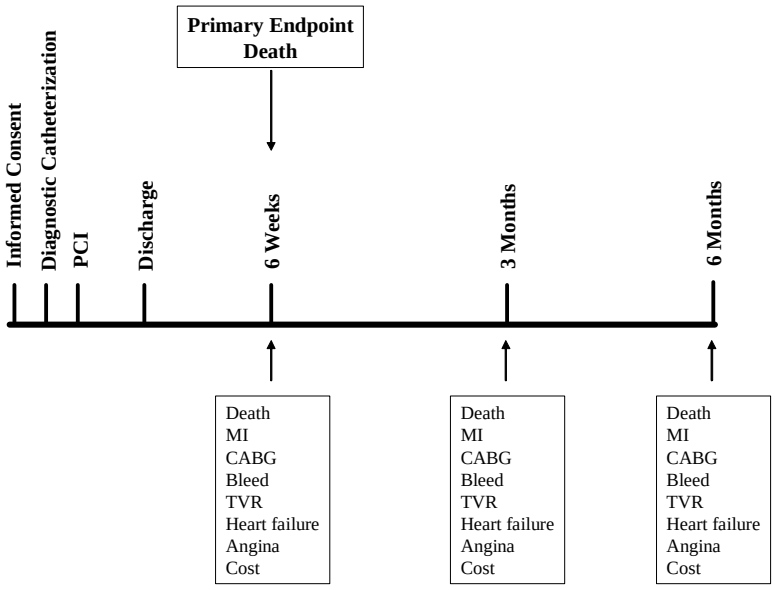
All aspects of the informed consent must be reviewed and considered in detail by potential study-subjects. Patients will be informed of all the usual risks, benefits and indications for catheterization and possible PCI, the study protocol and its risks, potential benefits if any and alternatives. It is particularly important that the study subject know that (1) this is a research study, (2) elective PCI without SOS is not allowed in this State except as part of this study, (3) elective PCI is usually performed in hospitals with SOS because emergency heart surgery is sometimes required because of a procedure-related complication, although this is rare (about 1 to 2 per 1000 cases), (4) if they do require surgery, there is a plan in place for emergency transfer, (5) there is no guarantee they will have PCI at the participating hospital because CABG may be the best option for them, or because they are considered by their physician at ‘high risk’ for a complication, or if they require treatment not available at the participating hospital: in that case, they will be transferred to a tertiary hospital for additional care and will not be randomized, (6) their medical information and the cost of their care including medical bills will be shared with researchers involved in the study, but will be kept strictly confidential.

Signed consents must be copied and the original placed in the patient chart, and a copy given to the patient and one kept for study records. In addition, signature pages for all consents are entered into the Sextant database and associated with the study registration case report form.

All individuals obtaining informed consent must be approved by their local IRB and must complete all required courses in informed consent procedures, HIPAA issues and human investigation as required by the local IRB.

8 - Schedule of Patient Contacts

Data for each patient will be gathered during initial hospitalization (index hospital and transfer hospital, if applicable) until discharge, and at 6 weeks, and 3, 6 months, as shown in the accompanying schematic.



Hospital Data: All in-hospital data are gathered by nursing staff at the participating hospital. Initial data are obtained within 24-72 hours of admission; subsequent data are gathered at the time of discharge or within 48 hours after discharge.

Because one of every 4 enrolled patients will be transferred to a hospital with SOS for PCI and will be discharged from that site, it is critical to establish formal ties between the participating site study coordinators and individuals at the hospital(s) with SOS to which patients may be transferred so that required medical information can be obtained in a prompt and reliable fashion.

During the initial hospitalization, the patient will meet local study staff so that follow-up contact can be explained. This should occur prior to the diagnostic catheterization since 25% of patients will be sent to a hospital with SOS for PCI. The patient should know that medical information from other healthcare providers and facilities may be obtained for the 6 months after the index procedure and that study personnel will be contacting him by phone at 6 weeks, and at 3 and 6 months after the index procedure.

Follow-up Data: Patients will be contacted by telephone (and/or mail, if necessary) by the participating hospital staff at 6 weeks, and 3, and 6 months after study entry to identify and define interval events. Medical records required to document identified events and cost data will be obtained as needed.

9 – Data Collected on Study Subjects

Data Elements: Elements in this table represent data to be collected on all patients. Data elements in this table will not necessarily be organized in this fashion, are not detailed (eg. some 'elements' may require several elements to define – eg. high and not-high risk lesions) and all elements to be collected are not represented in this table.

To the extent possible, data element definitions will follow those of the ACC- NCDR Cath Lab Module v 3.04.

Demographics	
	Name, address, phone number(s), social security number,
	Primary and secondary insurance carrier, account number, subscriber name
	Medical record number, medical account number
	Hospital name
	Age, gender, race
Admission Information	
	Source(inpatient, outpatient, emergency room, transfer)
	Status (STEMI*, NSTEMI, ACS, stable angina, atypical angina, no symptoms)
	Times for STEMI*/NSTEMI (symptom onset, ED arrival time (if transfer, arrival time at initial ED))
CAD Risk	
	Hypertension, hypercholesterolemia, diabetes, smoking (current, former, never)
	Height, weight
Specific Hx	
	Angina – Seattle Angina Questionnaire
	NYHA Class – 5 question set (Johns Hopkins Telewatch System)
Cardiac History	
	Prior MI, prior PCI, prior CABG, stroke, peripheral vascular disease, cerebrovascular disease, history of heart failure, family history of CAD, recent EST (outcome)
Other History	
	Renal failure, pulmonary disease
Admission PE	
	Height, weight, blood pressure, heart rate, S3, rales
Laboratory	
	Pre-catheterization serum creatinine (date, time, level, normal ranges)
	Serial CK, CK-MB, troponin (date, time, level, normal ranges)
	EST (latest, if any within previous 3 months) – and results
	LV function assessment (if any, with date/time)
Cath/PCI Procedure Status	
	Elective, urgent, emergent, salvage

	IABP
	Access (femoral, brachial, radial)
Dx Cath Findings	
	Nos. vessels > 70% stenosis, LV function (EF, if measured)
PCI	
	Segment, lesion severity (pre,post), TIMI flow (pre, post), r/o "type C" questions, device(s) used, PCI complications (no reflow, dissection, closure, perforation), closure device
	STEMI*/NSTEMI (clock start time, cath lab entry time, balloon inflation time)
Clinical Outcomes	
	Death, MI, CABG (emergent, any), stroke, bleeding (RBC transfusion),
	Heart failure (occurrence and class-Hopkins Telewatch Questions), angina (occurrence and class-Seattle Angina Questionnaire)
	Target vessel revascularization, any additional PCI
Economic Outcomes	
	UB92 (for insured patients) and itemized bill for all hospitalizations
	Other in patient costs (rehab, nursing home) – *estimated using Medicare Cost Report per diems*
	Physician/Technical services – *estimated based on identifying services and assign costs using Medical Fee Schedule*
Angiography	
	Pre and post PCI lesion(s) percent diameter stenosis (visual estimate)
	Pre and post PCI TIMI flow grade
	Dissection, thrombus,
	Device(s) used, drugs used, procedural ACT, ACT at sheath pull, closure device used
	Other vessel disease >70% severity
Follow-Up	
	Clinical outcomes (death, MI, CAB, TVR, etc – see above)
	6 weeks, 3 and 6 months
Supporting Documentation	
	Death – death certificate, death note, SSDI report; narrative description; reports
	MI – serial biomarkers with date/time (CK, CK-MB, troponin), serial ECG with date/time, narrative description; reports
	CABG – operative report; narrative description; discharge summary
	Heart Failure – Johns Hopkins Telewatch Question Set, narrative description, admission/discharge summaries
	Angina – Seattle Angina Questionnaire, narrative description, admission/discharge summaries
	TVR / any revascularization – reports; discharge summary
	Bleeding – dated transfusion slip

	Informed consent signature page
	ECG(s) as required (eg. for STEMI, NSTEMI, procedure-related MI, etc)
	Treatment Times - Cath lab log sheet, ED admission notes (including triage sheet)
	UB92 (for insured patients) and/or itemized bill

*STEMI – not included in randomized portion of trial, but included in parallel registry

10 - Data Gathering Procedures

Data Gathering Responsibilities

Participating site study coordinators (at hospitals without SOS) have sole responsibility for gathering and entering data into the Sextant data management system. No individual at any affiliated tertiary hospital with SOS or any other healthcare facility or provider enters data into the database at any time. This means that all data coming from all sources, including hospitals to which study subjects (those randomized and those not randomized) are transferred is gathered by the participating site study coordinators (at hospitals without SOS).

Data will be gathered at the local site and entered into the Sextant data management system. Data are entered in two ways in Sextant: (1) completion of web-based case report forms and (2) scanning of required supporting documentation into the database. In addition, the Angiographic Core Laboratory will complete web-based case report forms and directly enter angiographic data.

Case Report Form (CRF) Completion

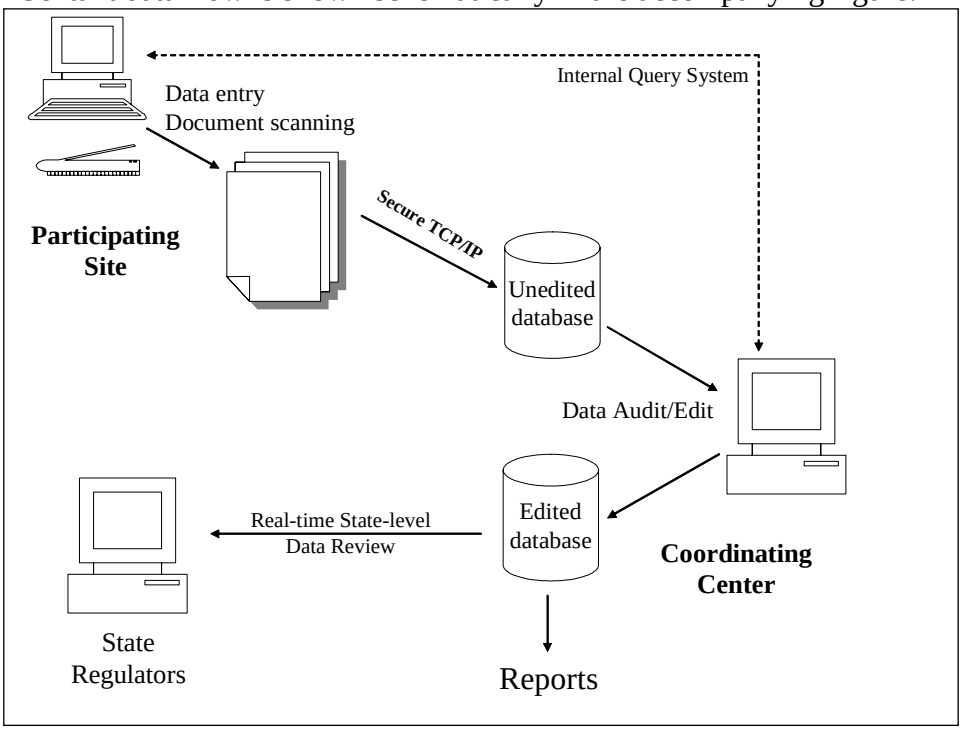
The "index hospitalization" includes hospitalization for the index procedure until the time of discharge from either the hospital without SOS or from the hospital with SOS if the patient was transferred to that hospital for ***any*** reason. CRF's related to the index hospitalization will be completed within 72 hours of patient discharge and will include data and outcomes from all sources.

Follow-up CRF's are completed by telephone interview at 6 weeks, 3 and 6 months.

Event CRF's for any event occurring during initial hospitalization or during the 6 week, 3 and 6 month follow-up period must be completed within 72 hours of occurrence. Events include but are not limited to death, recurrent infarction, stroke, bleeding, non-protocol angioplasty or angiography, and coronary artery surgery.

All data are entered into the Sextant data management system (see below) using web-based CRF's and scanning into the database any required supporting documentation appropriately censored of any private health information.

Data Gathering Instruments: Participating hospital staff will enter data in Sextant, a data management system. Sextant data flow is shown schematically in the accompanying figure.



Data are entered on electronic CRF's. CRF's may have a requirement to scan in and associate supporting documentation. For example, the Registration CRF requires scanning in the signature page of all informed consents. Once scanned into the database, the signed informed consent signature page is permanently associated with the Registration CRF. The Initial Hospital Data CRF requires scanning in of certain laboratory report sheets (e.g. documenting serum creatinine prior to catheterization). Once completed, CRF's and their scanned supporting documentation is locked by the

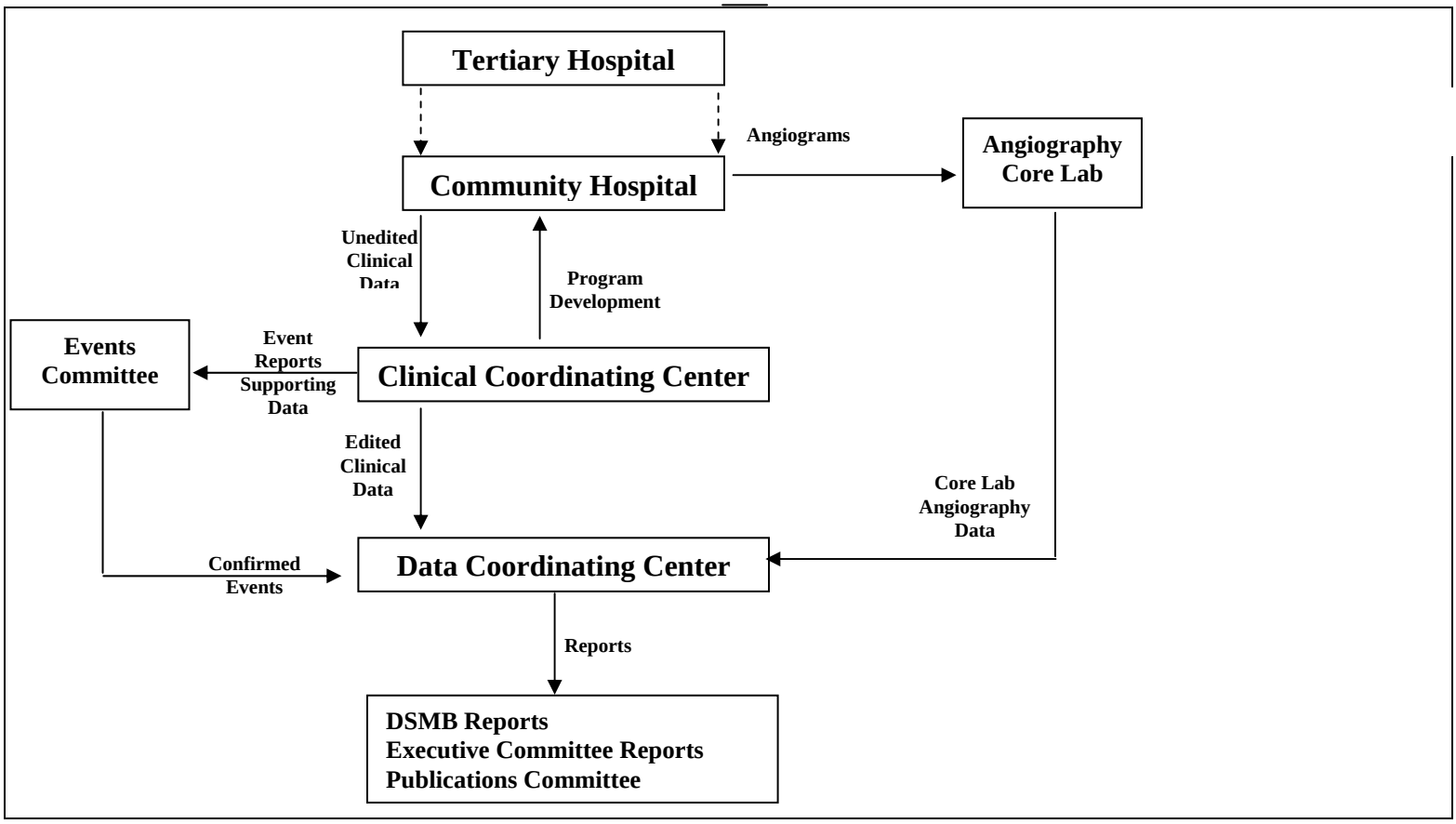
participating site coordinator and sent to the Coordinating Center for review. Data resides at this point in an 'unedited' database. Data in the unedited database are reviewed for completeness and for accuracy. If there are questions regarding a particular CRF, an internal query system allows communication between Coordinating Center and Participating Site personnel so that these issues can be resolved. CRF's can be unlocked for correction by Participating Site personnel, if appropriate (Coordinating Center personnel cannot alter CRF's). Once audited and edited as needed, data are 'certified' and permanently locked in an edited database.

Reports can be generated from the edited (and unedited) database for review (e.g. by the DSMB, Events Committee, etc). In addition, State regulatory authorities can have real-time, State-level data for review from any and all sites within their State for use in on-going quality assessment. These data are devoid of any private health information (e.g. demographics).

Participating sites personnel have access to their own local data through Sextant, as well, enabling creation of reports for quality assurance purposes throughout the study.

11 - C-PORT Organizational Structure

Overall Structure: The overall structure and data flow for proposed trial is depicted schematically in the picture below.



Each participating hospital assigns data collection duties to one or two clinical study coordinators. These individuals are responsible for completing case report forms, copying relevant parts of the documentation including consents and required parts of the medical record, and storing these locally. Each participating hospital identifies a economic study coordinator. This individual is responsible for gathering all required billing information. ***In addition, the clinical and economic study coordinators are responsible for obtaining required data from tertiary hospitals to which the patient subjects are transferred during initial hospitalization and during the 6 months of follow-up. No case report forms are completed and no data are gathered by staff at the tertiary hospitals: all data gathering, form completion, data storage and data transmission are done by the study coordinator(s) at the hospitals without SOS to which the patient initially presents.***

The Clinical Coordinating Center is charged with administering the angioplasty development program at participating hospitals. Program development details are reviewed in the section entitled "Coordinating Center Procedures" found elsewhere in this document. Clinical Coordinating Center personnel audit case report forms, review all potential events and prepare documentation for review by the Event Committee.

The Data Coordinating Center is charged with receiving and analyzing audited and edited data, preparing reports for the Data and Safety Monitoring Board, generating quality indicator reports for the Study Director and the Executive Committee of the Study, and generating reports for the Publication Committee, when required.

The Duke EQOL Coordinating Center is charged with entering Medicare Cost Report information, applying the appropriate Medicare Fee Schedule charge to physician and technical services and analyzing the economic data.

The angiographic core laboratory will enter data directly into the database.

12 – Coordinating Center Procedures

The Clinical Coordinating Center for the project is at the Johns Hopkins Medical Institutions. Coordinating center procedures are described in what follows.

The primary functions of the Coordinating Center are

1. project design
2. project implementation and execution
3. participating site development, implementation and execution procedures
4. deployment and maintenance of project data management tools (Sextant)
5. cooperative interaction with State agencies (Departments of Health)
    a. obtain waivers for project participation
    b. regular outcomes review
    c. provision of real-time, patient-subject outcomes data for State monitoring
6. angioplasty development program design and implementation at participating sites
    a. primary PCI development program
    b. elective PCI development program
7. development, implementation and coordination of project Committees that include
    a. Data and Safety Monitoring Board
    b. Substudy Committee
    c. Publications Committee
    d. Steering Committee

Participating Site Personnel Staff Training

All study personnel involved in data collection will be trained by supervisory personnel (principal investigators and senior nurses) before beginning actual data collection.

Data Handling Procedures

The CPORT organizational structure for this trial is shown in the figure in Chapter 11. Clinical and economic data are sent to the Clinical Coordinating Center from two field sources: the community hospital (without SOS) and the tertiary hospital. These data (case report forms and required supporting documentation) are reviewed by Clinical Coordinating Center staff. If data are correctly entered along with required supporting documentation then that record (study form) is certified (and locked) and sent to the Data Coordinating Center.

Angiograms are sent directly to the Angiographic Core Lab from the participating sites. The angiograms are reviewed and data are entered directly into Sextant database. The Clinical Coordinating Center reviews entered data and certifies it as complete before forwarding the data to the Data Coordinating Center.

Missing data reports can be created locally (at the participating site) in Sextant. Queries can be created for specific case report forms within Sextant, as well.

Reports for Committees (eg. the DSMB) are created through Sextant by the Data Coordinating Center.

Patient identification data will be kept on a separate form within Sextant, with the patient study identification code providing a link between that code and the patient's identity. ***All patient information data are kept strictly confidential.*** Access to medical records and any study database is on a need-to-know basis only and can be restricted

within Sextant to certain individuals. Access to Sextant itself is username and password protected and all activity is kept in a permanent audit log.

Copies of data forms and records will be stored at the participating hospitals, as well. These data will be placed in a folder for each patient.

Study Staff On Call

A study physician will be on call at all times to answer questions that may come up in the course of the trial. This physician-investigator can be reached through the **C-PORT trial principal investigator study pager number: 1-410-283-3660.**

I. Clinical Coordinating Center

Elective PCI Development Program: An elective PCI development program will be created and implemented as part of this project. Some of the methods and content can be taken from the current C-PORT primary PCI development program, but additional resources will be required. The program outline will include the setting of standards (for practitioners, institutions, facilities, care and staff competency), training of staff (observational, didactic and hands-on as required), development of logistics (particular attention to development of formal tertiary hospital and EMS affiliations for patient transport) and development of a quality and error management program (consisting of data collection and review, monthly staff QA meetings and weekly M&M in a cath conference setting, development of credentialing criteria).

Formal agreements between the participating site and both a tertiary facility willing to receive and an ambulance company capable of transporting any study subjects requiring emergency transport for tertiary-level care for any reason. A proven plan must be in place for emergency transport of a study subject from a hospital without to a hospital with SOS within 60 minutes of a call for such transport. The plan must be practiced and documented every 6 months.

Similarly, an important element of the program is related to minimizing the risk of coronary perforation and minimizing its impact should it occur (see Appendix materials). To this end, all participating facilities and practitioners will be required to train for use of the JoMed covered stent. In addition, all participating physicians will learn how to occlude distal coronary perforations using embolization techniques (coils, glue, etc). The plan of action for managing perforations including ambulance transport, operating room notification, reversal of anticoagulation, periocardiocentesis techniques including auto-transfusion, and use of sealing technologies (covered stents and embolization techniques) will be written, detailed and practiced every 6 months. Competency will be maintained by twice-yearly review and retraining.

Protocol: The project will require approval of each participating institution's IRB. Informed consent specific to this protocol will be obtained from each participating patient.

A requirement of all centers will be completion of a formal elective PCI development program.

In keeping with a patient-outcomes oriented project, there will be no or minimal protocol-required care. Application of institution, physician, device and patient selection criteria, data collection and informed consent are the only study requirements. Patients will be identified as potential candidates by matching with pre-specified inclusion and exclusion criteria. The principle or co-investigator will obtain informed consent from the patient. Two data collection personnel will be trained to collect, enter and transmit data, both case report forms and any required supporting documentation from the medical record.

PCI will be performed and conducted by the interventionalist, with no protocol-required care. The only limitations are those imposed by the available equipment, which itself is selected as described above.

Study Committees

Steering Committee
Executive Committee
Operations Committee
Event Committee
Publications Committee
Data and Safety Monitoring Board

The Steering Committee will be made up of Principal Investigators from each of the participating centers. The Executive Committee will be a subset of the Steering Committee made up of members interested and capable of more frequent meetings (eg. every other month) than required for the Steering Committee. The Operations Committee will be a subset of the Steering Committee handling day-do-day operations of the clinical trial. Except for the Data and Safety Monitoring Board, committee membership may include participating or non-participating investigators, physicians, nurses and others involved in the C-PORT trial. Members of the Data and Safety Monitoring Board (DSMB) will not be participants in the trial.

DSMB: The DSMB will consist of physicians, clinical trial specialists and at least one statistician and one bio-ethicist. The DSMB will have a first meeting at which operational aspects will be discussed including scheduled meeting frequency and stopping rules for the project. It is anticipated trial results may be reviewed at the first and second 4000 patients recruited into the study and then a final meeting at trial completion.

Emergency meetings of the DSMB may be required to review major adverse events, particularly death, that may be procedure-related. These emergency meetings will require a quorum of the DSMB and will be conducted via conference call.

Event Committee: The Event Committee is charged with reviewing all potential major outcomes including death, CABG, myocardial infarction, and stroke. Particularly for death and CABG within 24 hours of a procedure, the Event Committee will be required to adjudicate whether the death was definitely, probably or possibly related to participation in the project or the procedure, itself. All such events will be adjudicated by the Event Committee within 72 hours. Adjudication requires review and disposition of 2 members; if there is a difference of opinion regarding adjudication, a third member will review and all three reviews will be considered by the Event Committee Chair or Associate-Chair who will make a final determination. That final determination will be sent to the Chair of the DSMB who will, in turn, decide whether an emergency meeting of the DSMB is required. The meeting will be completed and the adjudication reviewed within 72 hours of the Event Committee determination. The DSMB will recommend either continuation of the trial, continuation of the trial but require additional review, suspension of the trial permanently or for additional review, suspension of trial activity by a specific site or practitioner, or any other action it deems appropriate in response to the event.

Core Labs

All qualifying ECGs will be reviewed for appropriateness of study entry by the Clinical Coordinating Center investigators. Discrepancy between the Center and the participating hospital interpretation will be resolved by the study director.

All cineangiograms will be forwarded by each participating site to the core angiographic laboratory. The cineangiograms will be evaluated from single views and the following data recorded: pre and post PCI diameter stenosis, pre and post PCI TIMI flow grade, estimate of other-vessel CAD (1, 2 or 3 vessel and left main disease), angiographic complications and lesion risk (ACC/AHA and SCAI risk classifications).

13 - PCI Program Development

The C-PORT PCI development program is usually a 3 to 4 month effort that involves many individuals at multiple levels at the participating hospital. Individuals involved include administrators, physicians, nurses and technical staff. This is a very detailed and detail-oriented undertaking involving multiple care areas within the institution including the emergency room, catheterization laboratory, coronary care unit and step-down unit. It is impossible to detail this program within this Manual. Overall, program development includes setting of standards, training of staff, development of local logistics, development of a quality and error management program that provides for a high-quality program both during implementation and after completion of the clinical trial. A summary outline is presented below.

I. Standards

Facilities: Hospitals should be performing *primary* PCI's per state guidelines, including both thrombolytic-eligible and thrombolytic-ineligible patients. While local state regulations may provide alternative minimum numbers, in no case should the number of primary PCI performed fall below 36 per year, the ACC/AHA guideline. While primary PCI patients are *not* randomized in the trial, outcomes data are placed in a parallel registry.

Hospitals should be performing a minimum of 200 non-primary PCI's per year. State regulations may provide alternative minimum volume numbers for specific reasons (eg. geographic isolation) or may allow a more gradual "ramping up" during the initial phase of the trial.

Care Providers - general: The employment and privileges granted to physicians and nurses at a facility certified by the State will serve as evidence of competence of physician and nursing personnel practicing in each of these environments. This ensures that community standards are applied where no national standards exist.

Care Providers - interventional cardiology: The American Heart Association/American College of Cardiology Joint Task Force guidelines for percutaneous transluminal coronary angioplasty serve as the basis for practitioner standards.

These standards set an average of $\geq$ 75 angioplasty cases per year as the minimum number required to maintain clinical competence. Therefore, the C-PORT trial will require that practitioner-investigators perform an average of 75 or more angioplasty cases per year.

Laboratory Standards:

The guidelines and policies defined by the Society for Cardiac Angiography and Intervention guide development of laboratory standards. All centers involved will have as a minimum a diagnostic cardiac catheterization laboratory. The existence of such a catheterization laboratory and its certification by the State of Maryland will constitute evidence of adequacy as a catheterization laboratory.

In laboratories in which coronary angioplasty is not currently performed, these laboratories must meet the following requirements:

i. documentation of *adequate training of catheterization laboratory staff*, including nurses and technicians
ii. documentation of adequate training of physician-practitioners
iii. documentation of *adequate supplies*

iv. documentation of *adequate support facilities*
v. completion of any required program development (for primary and elective PCI)

II. Training

Catheterization Laboratory Staff: Employment of staff (nurses and technicians) at a State-certified diagnostic catheterization and/or angioplasty laboratory will constitute evidence of competency to work in a diagnostic cardiac catheterization laboratory.

Hospital Staff: In hospitals in which angioplasty is *not* currently performed, the nursing and technical staff in both the catheterization laboratory and in the pre-procedure and post-procedure care units require additional training. This training is part of the primary and elective PCI development program.

Additional training includes familiarization with: angioplasty equipment (guide catheters, guide wires and angioplasty catheters including balloons and stents, distal protection devices, closure devices); commonly used drugs, such as heparin, clopidogril, and GpIIb/IIIa antagonists, assessment and monitoring of the state of anticoagulation; intra-aortic balloon counterpulsation equipment; patient transfer to and from the laboratory; and the multitude of issues related to pre-procedure, intra-procedure and post-procedure care. Development of algorithms for care of the patient who sustains a coronary perforation or who requires emergency cardiac surgery will be developed and practiced.

The C-PORT trial has developed a formal training program for technical and nursing staff working at hospitals without angioplasty capability. At a minimum this training will include:

1. one day didactic presentations and workshop ("Crew Conference)
2. minimum of 2 days (8 hours) of "one-on-one" observational training for all nurse-level caregivers in the catheterization laboratory and post-procedure care area (CCU and step-down unit) and catheterization technical staff at an affiliated tertiary facility
3. detailed development of hospital policy and procedures in the emergency room, cardiac catheterization laboratory, step-down unit and coronary care unit for patients with acute myocardial infarction treated with primary angioplasty and for elective angioplasty patients
4. detailed development of the logistics required to assure prompt, appropriate and effective application of primary angioplasty and elective angioplasty
5. detailed development of order sheets and checklists used in the care of PCI patients
6. detailed development of a quality and error management strategy for each participating institution
7. minimum one "dry run" or "run-through" by study staff at the participating hospital supervised by the Study Director and Study Nurse Coordinator for primary angioplasty
8. minimum one "dry run" by study staff at the participating hospital supervised by the Study Director and Study Nurse Coordinator for coronary perforation and emergency ambulance transport
9. regularly scheduled meetings among Coordinating Center staff and representative of involved departments (including nurses, physicians and technicians) for the duration of study enrollment to discuss study progress and identify and address problem areas, changes in protocol, and new treatment strategies or methods.

These elements are supplemented with vendor-supplied in-services and other continuing education programs.

Catheterization laboratory technical staff, catheterization unit nurses, and step-down and CCU unit nurses from each participating institution that currently does not perform angioplasty must attend (1) and (2) above. Participation of as many staff members from each institution is strongly encouraged.

If a member of the nursing or technical staff is to serve as a "second operator" during the angioplasty procedure, that individual must undergo additional training. This training requires "hands-on" experience performing elective angioplasty at a tertiary center under the supervision of the local principal investigator from his or her institution or his designee. Competence to perform as second operator will be determined by the training physician. Participation in at least 25 elective angioplasty procedures at a tertiary institution before assisting in a procedure performed at the participating site is a suggested guideline.

Completion of training procedures does not constitute certification of competency by any individual, institution or the C-PORT study staff of any individuals completing that training. Training means only that certain material has been reviewed and does not attest to the competency or experience of any individual undergoing that training.

III. Logistics

Care Plan Development: An important factor in the successful development of primary and elective angioplasty capability in a hospital which does not currently perform angioplasty involves nursing care. Familiarity with the course of the angioplasty procedure itself, the devices, including stents and drugs, including GpIIb/IIIa antagonists, utilized, anticoagulation regimens and their management, potential procedure-related complications, sheaths and intra-aortic balloon pumps, closure devices, and all the many pre-procedure, intra-procedure and post-procedure care issues is critically important to successful development of safe and effective angioplasty capability. While there is no substitute for experience, the didactic and observational training required for participation facilitates the transition to a PCI-capable facility.

Development of pre-procedure, intra-procedure and post-procedure nursing care plans and critical pathways is also important to successful management of the angioplasty patient. Care plans and pathways and staff training (including definition of competency requirements and competency maintenance) must be in place before angioplasty begins. Sample plans and critical pathways are reviewed at staff training sessions and are available from the C-PORT trial staff.

C-PORT study personnel assist participating hospital technical and nursing personnel develop detailed care plans and pathways for angioplasty patients. Model care plans and pathways are provided by the Clinical Coordinating Center and modified by the participating hospital staff as appropriate for their facility. This is done through direct contact supplemented by email, telephone and fax communication over a several week (typically 12-14 week) period. Formal and informal discussions and meetings between study personnel (particularly the nurse coordinator) occur during this period concerning pre-angioplasty, intra-procedure and post-procedure care, sheath pulling, monitoring, and complications, as care plans and procedures are developed at the participating institution. Subsequently, at least weekly contact is continued to answer the many questions and address the many issues that require resolution during initiation of a new clinical program and commencement of a clinical trial.

Logistics Development for Primary PCI: For hospitals not currently performing primary PCI, that program must be established prior to beginning the non-primary PCI randomized trial. This requires development of detailed, local logistics. The logistical goal is for all patients to have primary angioplasty within 90 minutes of Emergency Room arrival. The specific issues that must be addressed to assure the prompt, appropriate and effective application of primary angioplasty in the treatment of AMI is the goal of logistics development. The specific plans required in each participating institution are specific to that institution, although the goal remains the same. Logistical issues that need to be addressed include: hours of operation, who obtains consent, mechanisms to gather staff, mechanisms to assure availability of staff and catheterization laboratory, plans for recurrent ischemia or infarction, plans to determine the responsible physician during and after the primary angioplasty, plans for failed angioplasty, fall-back plans for primary angioplasty system failure, and many additional issues. These are all addressed during the primary

angioplasty development program.

Logistics Development for Elective PCI: A critical aspect of elective PCI development at hospitals without SOS is creation of detailed algorithm for management of coronary perforation and for emergency transfer of patient who require care at a tertiary facility for any reason. Algorithms for management of both coronary perforation and emergency transfer are created and practiced during the PCI development program. Continued practice during the course of the clinical trial is mandatory, involves the entire catheterization laboratory staff and takes place at least every three months.

On-going training: After trial start-up, on-going supplementation of initial training with frequent face-to-face meetings and telephone contact with nursing and physician study personnel continues. Experience to date suggests that at study initiation frequent telephone contact is required; after several weeks, contact is less frequent but is maintained as needed by telephone and/or email. Regular meetings between study personnel from the Coordinating Center and the participating facility to discuss identified problem areas, to resolve such problems, to provide on-going feedback regarding study progress and quality of care, and to provide on-going training in new techniques, drugs or procedures related to the treatment of PCI patients are important and occur at least every 6 months during the trial.

IV. Quality and Error Management

Quality and Error Management: An important aspect of the C-PORT primary and elective angioplasty program development alluded to above is quality and error management. Outcomes data are available to participating sites through the Sextant data management system, which is provided by the Clinical Coordinating Center. Review of outcomes on a regular basis is important to identify problem areas. Plans for addressing problem areas will be developed in collaboration with the Clinical Coordinating Center and plans for short and long-term monitoring to assess remedial efforts are made. Special emphasis is given to minimizing, discovering, reporting and correcting error in the system of PCI care developed at participating institutions.

Outcomes data are also available to State regulatory authorities for their State's participating institutions through the Sextant data management system.

Two important elements of quality and error management include creating a mechanism for local peer-review and on-going, regularly scheduled multiple care-area meetings.

Local peer-review (cath/intervention or "M&M" conferences) may be difficult to develop because of a small number of staff. An alternative to local peer-review is review of cases at the affiliated tertiary hospital's interventional case review meetings on a regular basis. Weekly peer-review (e.g. cath/intervention conference) is required at participating institutions. Attendance of at least 60% of such meetings by catheterization laboratory personnel (including physicians, nurses and technicians) is required for participation in the study.

It is important for physician, nursing and administrative representatives from the care areas involved in the primary and elective angioplasty systems (emergency room, catheterization laboratory, coronary care unit and step-down unit) to meet on a regular (eg. monthly) basis to improve procedures, identify problem areas and develop solutions, and to plan for continuing medical education for all groups. EMS and the affiliated tertiary hospital are important partners in this effort. Representatives from both of these groups should be encouraged to attend participating site care area meetings.

14 - Policy Matters

Ancillary Study Policy

Ancillary studies may be included at one or more participating C-PORT sites. Ancillary studies must not interfere with performance of the main clinical trial or in any way degrade patient care.

Ancillary studies must be reviewed and approved by the Executive Committee. Ancillary studies may originate from principal investigators, nurse coordinators, core laboratory personnel, participating physicians or staff at participating hospitals, third party payers or government health-care policy makers.

Formal proposals must be submitted in writing and include:

1. background information
2. the hypothesis to be tested
3. data to be obtained, including how it is to be obtained and by whom
4. the risks to the patient
5. potential interaction with the main protocol
6. needed changes to the informed consent procedure
7. statistical information: required sample size and data analysis plans
8. proposed collaborators and letters of agreement to participate from each
9. proposed writing group and Chairman
10. cost of the study and financial support available with appropriate documentation.

The procedure for submitting an ancillary study for review includes sending a formal proposal to the Study Chairman who will forward the proposal to the Executive Committee. The Executive Committee will review the proposal within four weeks and submit its recommendation to the Steering Committee for final review and adjudication.

Publication Policy

The development and execution of this trial will generate new data which may warrant publication. The C-PORT Publications Committee guides and facilitates development of reports involving the C-PORT trial. The Publications Committee will develop methods and standards for regular and timely evaluation of suggested topics for reports and the submission and completion of those reports for publication.

The Steering Committee and the Executive Committee will develop a series of reports and report topics based on the main trial or a formal ancillary study. Each report will have an associated writing group and a Chairman of that writing group developed by the Steering Committee or the Executive Committee.

In addition, investigators, study coordinators, involved staff (physician, nursing and technical) at participating institutions and participating ancillary centers are encouraged to suggest topics suitable for reporting. For each topic, a writing group should be developed with a designated Chairperson. The topic, the writing group and its Chairperson will be reviewed by the Publications Committee, revised as appropriate and forwarded to the Steering Committee for review and approval. Topics will be prioritized by the Publications Committee.

Development of a report topic proposal should include:

1. background information
2. the hypothesis to be tested or aim of the study
3. data that are to be used

4. statistical methods
5. proposed collaborators
6. proposed writing group and its Chairperson.

When two or more identical or similar proposals are submitted simultaneously or nearly simultaneously (within one month of each other), the Publications Committee will decide which group will be allowed to proceed with the report development or if all or some groups should be combined. The results of the Publication Committee's adjudication will be submitted to the Steering Committee for final approval.

Publications related to the C-PORT trial must be reviewed for timing, authorship and content by the Publications Committee prior to submission for publication.

The Publications Committee will use the following guidelines:

1. All reports that concern endpoint data must include data from all sites. In general, no single site reporting of data will be allowed.
2. All data reported must be reported without identifying patients, institutions or caregivers.
3. No "preliminary" results reporting will be allowed for the main study
4. For authorship, the individual must have made a substantial intellectual contribution to the development of the manuscript.
5. All reports should include "for the C-PORT Trial Group" at the end of the authorship list.

Conflict of Interest Policy

The C-PORT trial investigators endorse the 21st Bethesda Conference: Ethics in Cardiovascular Medicine and the NIH guidelines for conflict of interest.

Individuals who are governed by the C-PORT conflict of interest policy include the Study Chairman, all Principal Investigators for each project at each participating clinical center, nurse coordinators, core laboratory personnel, any other investigator or staff member who has a significant role in collecting and/or reporting of data for the trial. Physicians and staff who are involved with C-PORT and C-PORT participants primarily as care providers and who are not involved with the collection or reporting of data are not governed by this conflict of interest policy.

Guidelines begin at the start of patient recruitment and terminate at the time of initial public presentation or publication of the principal results. Investigators who discontinue participation in the trial during recruitment will no longer be subject to these guidelines after their departure from the study as long as they are not privy to endpoint data.

For the time period defined above, C-PORT investigators agree not to own, buy or sell stock or stock options in any pharmaceutical company or medical equipment company with products being used in this trial. Investigators also agree not to have a retainer-type consultant position with these companies for the time period defined above. Conflict of interest statements will be updated annually from each investigator. Financial interests in these companies over which the investigator has no control (mutual funds, blind trusts) do not fall under these guidelines.

Activities not explicitly prohibited, but to be reported annually to the Study Chairman and maintained in the conflict of interest file include:

1. ad hoc consultant relationships to companies whose drugs or equipment are used in the trial;
2. participation of investigators in any educational activities sponsored by such companies; and
3. participation of investigators in other research projects supported by such companies

In the case of actual or perceived conflict of interest, the Study Chairman will bring it to the attention of the Data and Safety Monitoring Committee and the Steering Committee for appropriate action. This may include removal of an individual as an investigator in the C-PORT study for irreconcilable conflict of interest.

Press and Media Policy

Distortions and misrepresentations of medical studies and results are not infrequent and can have unpredictable and often deleterious effects on the conduct of a trial and its integrity. The C-PORT trial discourages discussion of the C-PORT study - its methods, development or results - in the lay press, including print, radio, television, and electronic media. This is particularly true while the study is on-going, before all results concerning primary endpoints are completed.

Interviews or any other kind of report to the press (print, radio, television or electronic, including Internet or Web-based publications) before primary endpoint outcomes are made public and/or published may be harmful to the completion and interpretation of the C-PORT trial and are discouraged. No endpoint results including medical, economic and quality of life outcomes or complications should be discussed in the course of any interview until these results have been published or presented publicly. Interviews may not reveal results of any C-PORT-related study not already made public or already published.

Any breach of patient confidentiality through publication or in any other way constitutes sufficient grounds for termination of any participating investigator and/or institution from further participation in the trial. Potential violations will be reviewed by the Study Chairman and referred to the DSMB for final action before an investigator or institution is removed from further study participation.

No hospital, practice, or physician whose patients are enrolled in the trial may use the C-PORT trial name or logo that in any way promotes or appears to promote that hospital, practice or physician or the services they offer.

Policy Regarding State Regulations and Waivers

In several states, a waiver to regulations barring angioplasty at hospitals without cardiac surgical programs is granted so that the trial can be implemented. The specifics of the waiver are different in each state. This waiver pertains only to patients enrolled in the C-PORT trial who undergo angioplasty in accordance with the C-PORT protocol. The regulations barring angioplasty at hospitals without on-site cardiac surgery remain in effect, however, and do not allow performance of any non-protocol angioplasty at any hospital without an on-site cardiac surgical program.

Continued inclusion of a participating hospital in the C-PORT study requires adherence to the spirit and letter of state health-care regulations and the waiver granted by regulatory agencies in each state. Regular reporting of the course of the C-PORT trial, including adherence to the terms and conditions of the granted waiver, will be made to the Department of Health for each state in which there are participating sites.

Violation of the waivers or other health-care regulations constitutes sufficient grounds for termination of any participating investigator and/or institution from further participation in the trial. Potential violations will be reviewed

by the Study Chairman, result in immediate suspension and referred to the DSMB for final action before an investigator or institution is removed from further study participation.

15- Required Treatment

The C-PORT trial is a community-based, patient outcomes trial and as such mandates no protocol-required care.

Cardiac catheterization and angioplasty should be performed using standard techniques, procedures, catheters, devices and drugs as per local community standards. There are devices excluded from use at hospitals without SOS (see Chapter 4 above). The only C-PORT requirement is that no experimental or unapproved drugs, devices or procedures be used.

Similarly, patients cannot be involved in any additional research project which might affect their outcome.

16 - Guidelines for Clinical Care

All clinical care is at the discretion of the treating physician. The C-PORT project endorses the ACC/AHA guidelines for management of unstable angina and non-ST-segment elevation myocardial infarction and acute ST-segment elevation myocardial infarction, and guidelines for performance of percutaneous coronary intervention.

For patients not enrolled (consented) in the angioplasty trial at hospitals without on-site cardiac surgery, ***State regulations governing angioplasty remain in effect***. No patient at such a hospital should have an angioplasty at that hospital unless the treating physician believes that transfer to a tertiary hospital would be harmful to the patient.

17 - Start-up Procedures

Before Study Initiation

Before the C-PORT trial can begin the following certification procedures must be completed.

1. A formal agreement between the Clinical Coordinating Center and the participating hospital must be completed and signed
2. A formal agreement between the participating site and a tertiary hospital (with SOS) that provides that the tertiary facility will receive and care for any and all study subjects requiring emergency care of any kind
3. A formal agreement between the participating site and an IABP and ACLS capable ambulance service that provides that service can respond to a call within 30 minutes and transport patients to the receiving hospital within 60 minutes
4. Study staff must be identified
    i. Physician principal investigator and all sub-investigators
    ii. Clinical and economic study coordinators
    iii. Participating site administrative contact
5. Sextant data management system must be installed and functional
    i. Secure PC running Windows 98 or above as OS
    ii. High-speed internet connection with port 1433 open for outbound traffic
    iii. Attached multi-page, twain-compatible scanner
    iv. Installed and functioning Sextant software
    v. Training of all Sextant users
    vi. following IP address needs to be accessed: 162.129.119.234
    vii. port 80 (web traffic) must be available for the auto-update feature
6. Training of clinical and economic study coordinators
    i. study data definitions
    ii. supporting documentation required
    iii. follow-up requirements and practices
    iv. development of formal tertiary hospital contacts for clinical and billing information
    v. timeline for forms completion
    vi. use of Sextant
    vii. successful completion of NIH-sponsored human subject training at http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp
7. at centers without current primary angioplasty capability,
    i. all hospital staff must complete the required primary angioplasty development program
        i. nursing protocols and care plans must be in place and reviewed
        a. logistics and a written logistical plan must be in place
        b. quality and error management procedures must be reviewed and agreed upon by the Clinical Coordinating Center and the participating institution
        c. one dry run or run-through must be performed with study staff
        d. documentation (a list) of available angioplasty equipment must be submitted to the Clinical Coordinating Center and reviewed by study staff

8. at centers with primary PCI capability
    i. all cath lab staff (physician, nursing and technical) must complete the elective angioplasty development program which includes but is not limited to
        a. nursing protocols and care plans must be in place and reviewed
        b. program development in the step-down (post-procedure) unit must be completed
        c. logistics and a written logistical plan must be in place
        d. quality and error management procedures must be reviewed and agreed upon by the Clinical Coordinating Center and the participating institution
        e. algorithm for care of the patient requiring emergency CABG must be developed and practiced
        f. algorithm for care of coronary perforations must be developed and practiced (see appendix)
9. participating physicians must fill out the **C-PORT Investigator's Worksheet** (sample in appendix), documenting name, address, methods of communication, and, if performing angioplasty as part of this trial, the number of angioplasties performed in the past year or average yearly angioplasties performed
10. the site principal investigator must fill out the **C-PORT Logistics Worksheet** (sample in appendix) detailing local procedures for patient identification, data management, obtaining consent, etc.
11. a copy of the local IRB-approved consent form and the letter documenting local IRB approval of the C-PORT trial must be sent to the Clinical Coordinating Center

Study Initiation

After completion of the first ten patients, recruitment is suspended and data from these patients is reviewed. Quality management strategy requires review of both outcomes and process quality indicators. Careful review of adherence to study protocol and local logistics (process indicators), quality of care, angiographic and medical outcomes and complications (outcomes indicators), will be carried out and discussed with the local principal investigator. Steps will be taken to correct identified deficiencies.

If the local principal investigator and the Study Chairman agree that study goals have been achieved and patient care has been of adequate quality, then enrollment in the trial will resume.

18 - Angiography Core

The angiographic core is responsible for receipt, cataloguing, quantification, and returning of angiograms of patients enrolled in the C-PORT trial. Angiograms from a selection of patients from all sites will be reviewed by the core lab. It is estimated that approximately 50 total cases will be reviewed from each participating site: the first and the last 25 cases.

Guidelines for Coronary Angiography:

1. Catheters should be 6, 7 or 8 F.

2. The non-tapered aspect of the catheter free of contrast must be included at the start of each cine sequence.

3. Each coronary artery should be visualized in at least two views. Magnification should be selected so that most of the vessel can be visualized with minimal panning during the cine sequence.

4. For each injected vessel, 150 ugm of intracoronary (or intragraft) nitroglycerin should be given prior to the first cine sequence, unless the systolic blood pressure is <100 mmHg.

5. A cardiac catheterization log must be completed. The catheterization log must include
    i. the time of the procedure
    ii. all drugs used during the procedure (including time and route of administration and dosage)
    iii. catheters used for each sequence (French size, manufacturer and model)
    iv. all devices used during the procedure
    v. ACT's recorded during the procedure
    vi. the name of the operator
    vii. infarct-related artery (of any)
    viii. event timing (admission to cath lab, balloon inflation, etc)

If your institution does not routinely document this information, then please either modify local documentation procedures to include this information or use the supplied sample log sheets for documentation.

6. Post-angioplasty, the two views which best visualize the infarct-related artery must be repeated after removal of all equipment including guidewires.

Site Certification Procedures

These will be specified by the Angiographic Core Laboratory in a separate document.

QCA Core Lab Procedures:

Participating hospitals will:

1. agree to follow cine acquisition procedures
2. send films by to the Angiography Core on a regular (e.g. monthly) basis
3. maintain a log of all study films containing the patient name, local hospital number, date of procedure, date sent to Core, date received back from Core

The Core Lab will perform the following functions

1. receive, log in, store, all study cine films
2. identify and record pre- and post- angioplasty stenosis severity of the artery segment (using the ACC/AHA coronary segment definitions (1-15))
3. TIMI flow
4. angiographic success
5. angiographic complications
6. other vessel disease (>70%)
7. define the lesion risk category (A, B or C)
8. enter data into Sextant

QCA Methods

These will be defined in a separate document provided by the Angiographic Core Lab.

Data Submitted to the Data Coordinating Center:

The following data will be transmitted to the Data Coordinating Center:

1. identify and record pre- and post- angioplasty stenosis severity of the artery segment (using the ACC/AHA coronary segment definitions (1-15))
2. TIMI flow
3. angiographic success
4. angiographic complications
5. other vessel disease (>70%)

Ancillary Studies:

All ancillary studies using Core facilities or personnel must be approved by the Executive Committee.

17 - References

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3. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet. 2003; 361(9351):13-20.

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17. William D. O. NHLBI DYNAMIC Registry Outcomes Data (personal communication)

Appendix
Materials

C-PORT Logistics Worksheet

Principal Investigator: _____

Hospital: _____

For each response, please specify ***by name*** the MD, RN or other personnel who will perform this task. If multiple individuals perform that task, they all need to be identified. Questions ? Call 410-955-3996 or 410-955-5399.

Who will identify eligible patients and inform those who will obtain consent ?

_____
_____
_____

Who will obtain informed consent ?

_____
_____
_____

Will a diagnostic catheterization team be available to begin the procedure if an interventionalist is not available?

□ yes □ no

Who will determine if PCI can be performed?

_____
_____
_____

Emergency transfer arrangements:

ambulance company name:_____

coronary artery surgery facility:_____

How will you contact your angioplaster(s) and determine his availability ?

- direct pager
- g. operator-assisted page
- h. call to office
- i. other _____

Additional Personnel: *Please complete each section,* ***providing both name, email and phone number.***

Emergency Room:

Medical Director _____

Nurse Manager _____

Charge Nurse_____

Catheterization Laboratory:

Manager _____

Chief Technician _____

Head Nurse _____

CCU/ICU:

Medical Director: _____

Nurse Manager _____

Charge Nurse(s) _____

_____

Step Down Unit:

Nurse Manager _____

Charge Nurse(s) _____

_____

Pharmacy Director _____

Medical Records:

Director _____

CPORT Contact _____

Please mail or fax completed worksheet to the study coordinating center.

Thomas Aversano, M.D.
5501 Hopkins Bayview Circle
JHAAC Room 1B.40
Baltimore, MD 21224
FAX: 410-550-9081

C-PORT Investigator Worksheet

Please fill in requested information and return worksheet to T. Aversano MD, 5501 Hopkins Bayview Circle JHAAC Room 1B.40, Baltimore, MD 21224 OR FAX 410-550-9081

Name:_____

Institutions at which you have privileges :

1. _____ 4._____
2. _____ 5._____
3. _____ 6._____

Describe your *primary* practice type - check all that apply:

□ general internal medicine □ general cardiology □ emergency medicine
□ acute coronary care □ electrophysiology □ heart failure/cardiomyopathy
□ non-invasive □ diagnostic cath □ interventional
□ non-tertiary hospital □ tertiary hospital □ academic medical center
□ office based □ hospital based

Do you perform diagnostic catheterization ? □ yes □ no

If yes, approximate number of cases last year _____

Will you be doing C-PORT related diagnostic catheterization ? □ yes □ no

Do you perform angioplasty ? □ yes □ no

If yes, approximate number of cases last year _____

Will you be doing C-PORT related angioplasty ? □ yes □ no

<u>Preferred Contact Address and Phone Numbers</u>:

Street Address: 1. _____

2. _____

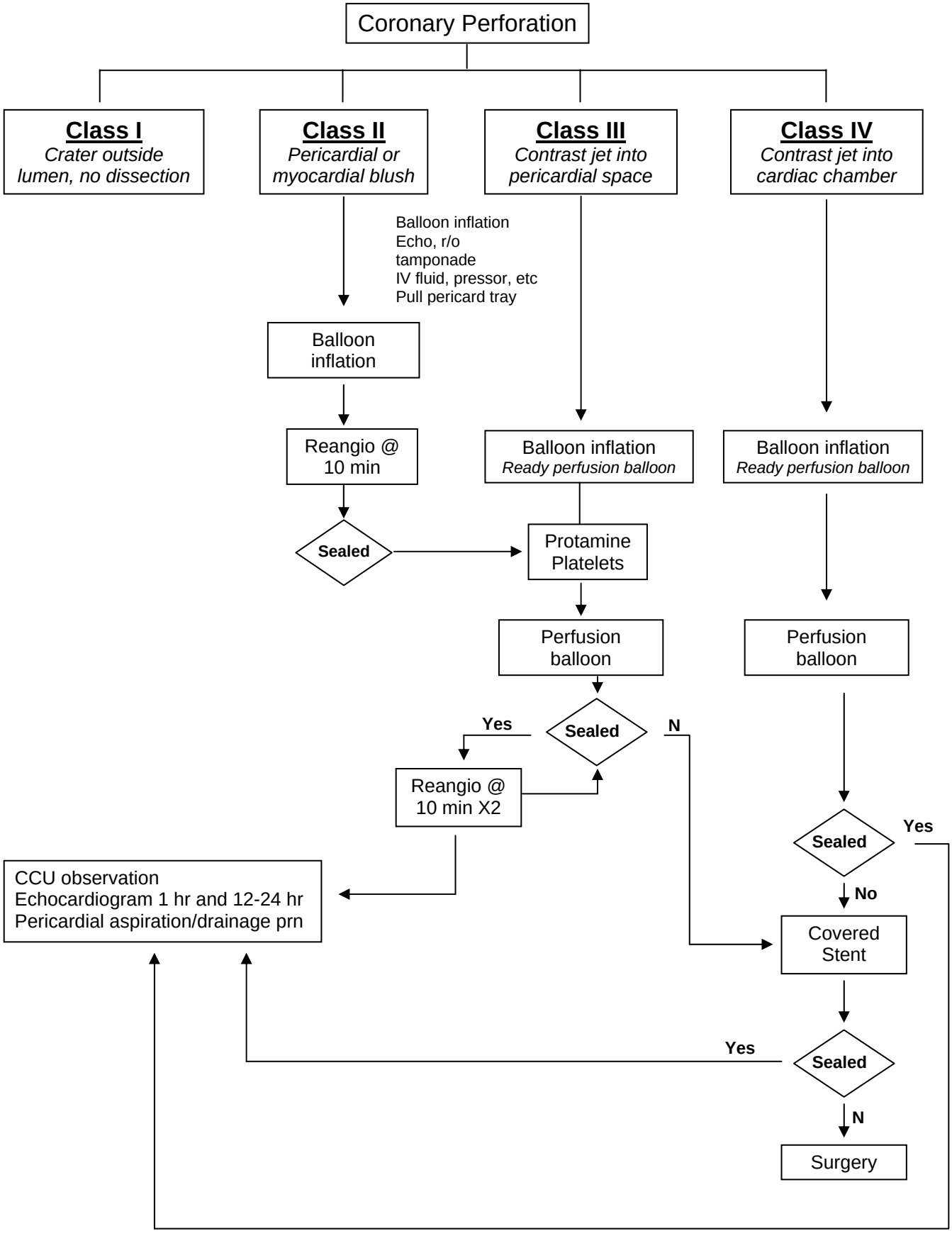
City _____ State ___ ___ Zip_____

Phone: _____-_____-_____ Alternate Phone: _____-_____-_____

FAX: _____-_____-_____ email address:_____

Secretary's Name _____

Your Signature: _____ Date _____


Coronary Perforation
Class I
Crater outside lumen, no dissection
Class II
Pericardial or myocardial blush
Class III
Contrast jet into pericardial space
Class IV
Contrast jet into cardiac chamber
Balloon inflation
Echo, r/o tamponade
IV fluid, pressor, etc
Pull pericard tray
Balloon inflation
Reangio @ 10 min
Balloon inflation
Ready perfusion balloon
Balloon inflation
Ready perfusion balloon
Sealed
Protamine
Platelets
Perfusion balloon
Perfusion balloon
Yes
Sealed
N
Reangio @ 10 min X2
Sealed
Yes
No
CCU observation
Echocardiogram 1 hr and 12-24 hr
Pericardial aspiration/drainage prn
Covered Stent
Yes
Sealed
N
Surgery

Coronary Perforation Checklist

Administrative Tasks:

- ☐ Call for stat 2-D echocardiogram (call ***** or ***-*****)
- ☐ Alert ambulance service for probable transport (call ***** or ***-*****)
- ☐ Alert cardiac surgery for probable transport (call ***** or ***-*****)

Clinical Tasks:

- ☐ **Class of perforation**
  - ____ Class I (extraluminal crater without dissection)
  - ____ Class II (pericardial or myocardial stain without contrast jet)
  - ____ Class III (jet of contrast into pericardial space)
  - ____ Class IV (jet of contrast into cardiac cavity)

Considerations

- ☐ inflate **current balloon** (5 to 10 min) (Class II, III, IV)
- ☐ Pull pericardiocentesis tray or materials
- ☐ Volume resuscitation, pressors ?
- ☐ D/C and/or reverse anticoagulation and antiplatelet agents

For Class III consider reversal of heparin with protamine

Time since heparin	Protamine dose
< 30 min	1 mg protamine / 100 IU heparin
30-60 min	0.5 mg protamine / 100 IU heparin
> 2 h	0.25 mg protamine / 100 IU heparin

Check ACT after protamine – aim for ACT $\leq$ 150 seconds

Antiplatelet agents

Consider stopping GpIIb/IIIa antagonists

Consider reversing GpIIb/IIIa antagonists

abciximab (ReoPro) – stop agent, platelet transfusion

epitifibitide (Integrilin) – stop agent, dialysis

- ☐ while current balloon inflated, ready **perfusion balloon** (Class III, IV)
- ☐ consider covered stent (JoMed Stentgraft)

- ☐ volume resuscitation, pressors?
- ☐ 2-D echocardiogram
- ☐ pericardiocentesis

Perforation management kit:

Perforation management algorithm
Perforation management checklist
Pericardiocentesis tray
Perfusion balloons
JoMed Stent Grafts
Protamine vials
Pressors